Three Ways Family Health History will be Crucial for Clinical Genomic Testing

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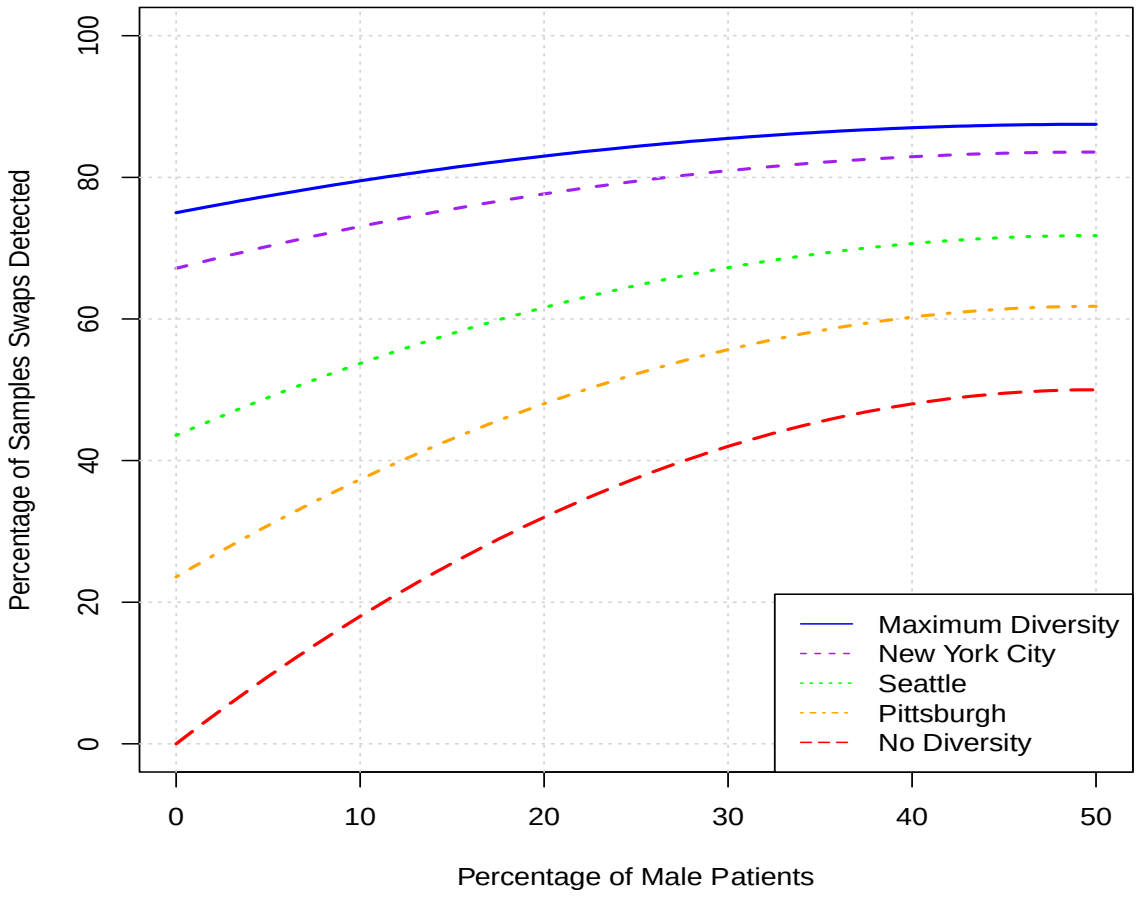
How Personalized is Your Medicine?

"Because we know about your unique genes we can tailor your treatment to avoid harmful medication side effects we have seen in others like you"

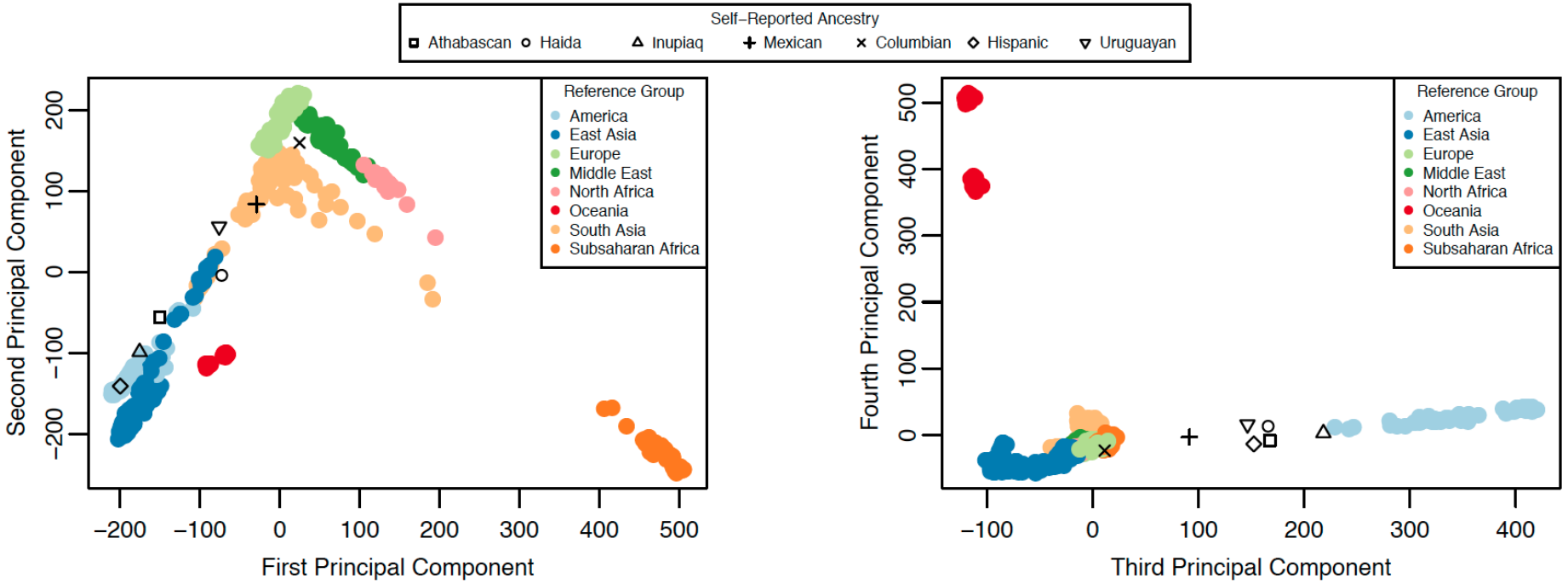
1. FAMILY HEALTH HISTORY CAN BE USED FOR GENOMIC QUALITY CONTROL

Using Family History for QC



Mathias PC et al. Applying Ancestry and Sex Computation as a Quality Control Tool in Targeted Next-Generation Sequencing" *Am J Clin Pathol. 2016 Mar;145(3):308-15*

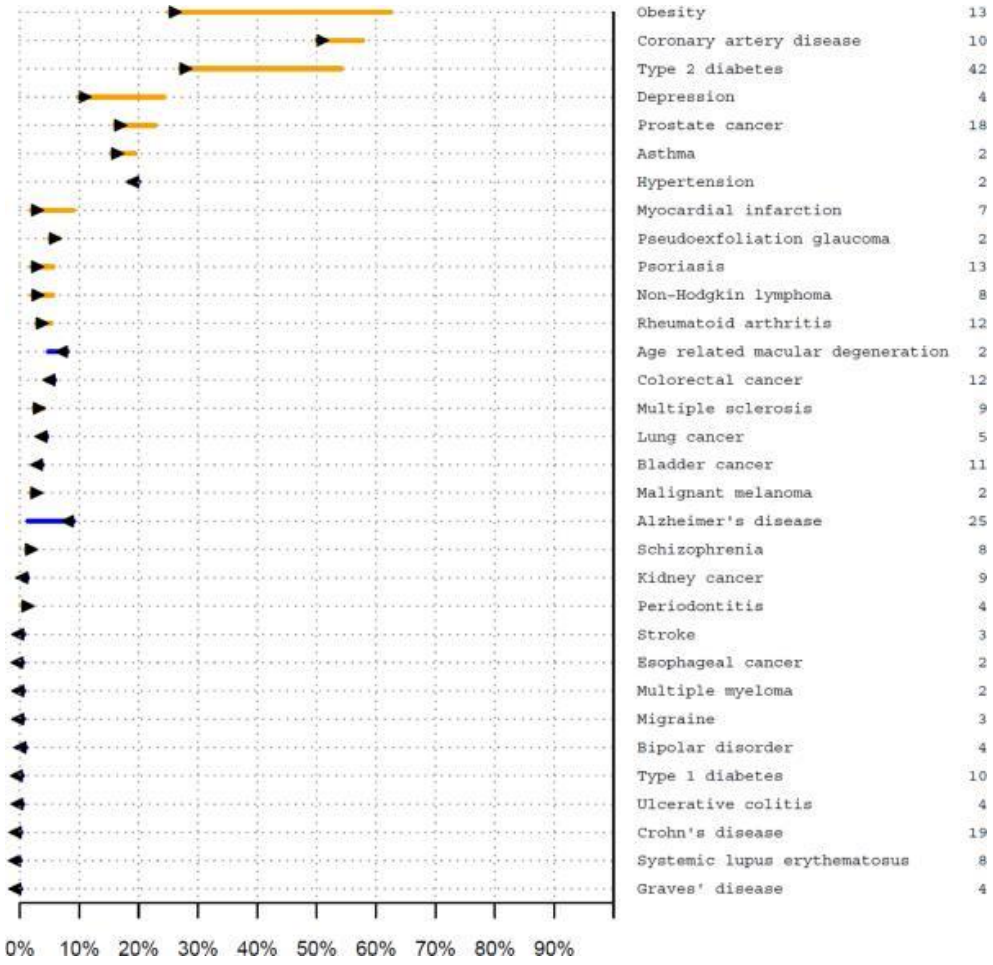
Using Family History for QC



Mathias PC et al. Applying Ancestry and Sex Computation as a Quality Control Tool in Targeted Next-Generation Sequencing" *Am J Clin Pathol. 2016 Mar;145(3):308-15*

2. FAMILY HEALTH HISTORY TO DRIVE CASCADE SCREENING

“The personal genome—the future of personalised medicine?”



Ormond et al: *The Lancet*, *Volume 375, Issue 9727*, *15–21 May 2010*, *Pages 1749-1751*
Challenges in the clinical application of whole-genome sequencing

Genes where a single inherited variant alters medical care

- *BRCA1, BRCA2, PALB2*
- *MLH1, MSH2, MSH6, PMS2*
- *LDLR, APOB, PCSK9, LDLRAP1*
- *APC, MUTYH, NTHL1*
- *PTEN*
- *ACVRL1, ENG, SMAD4, BMPR1A*
- *MYH7, MYBPC3, TNNT2, TNNI3*
- *DNAJC19*
- *HBA1, HBA2, HBB*
- And many more ….

Cascade Screening

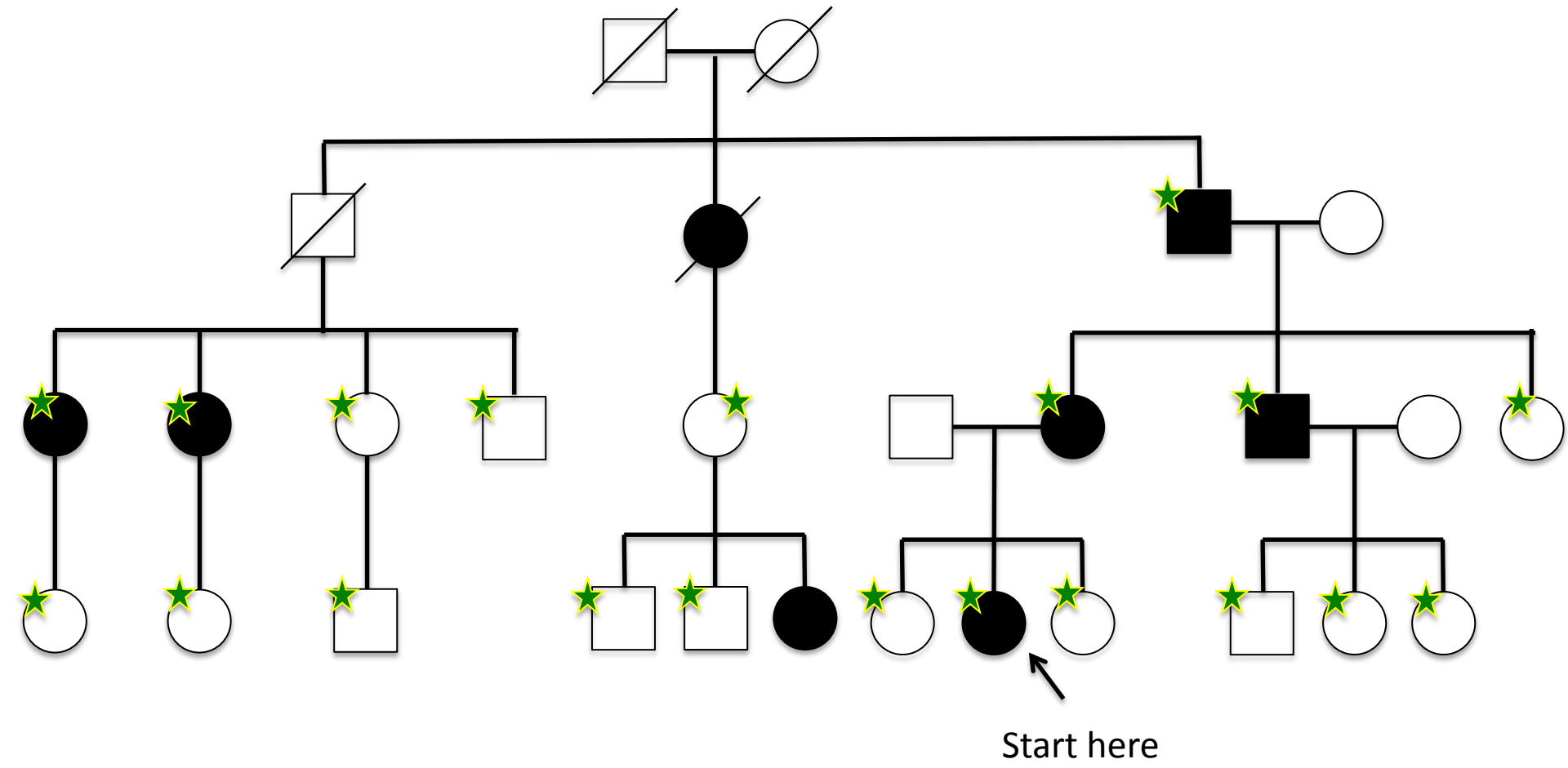
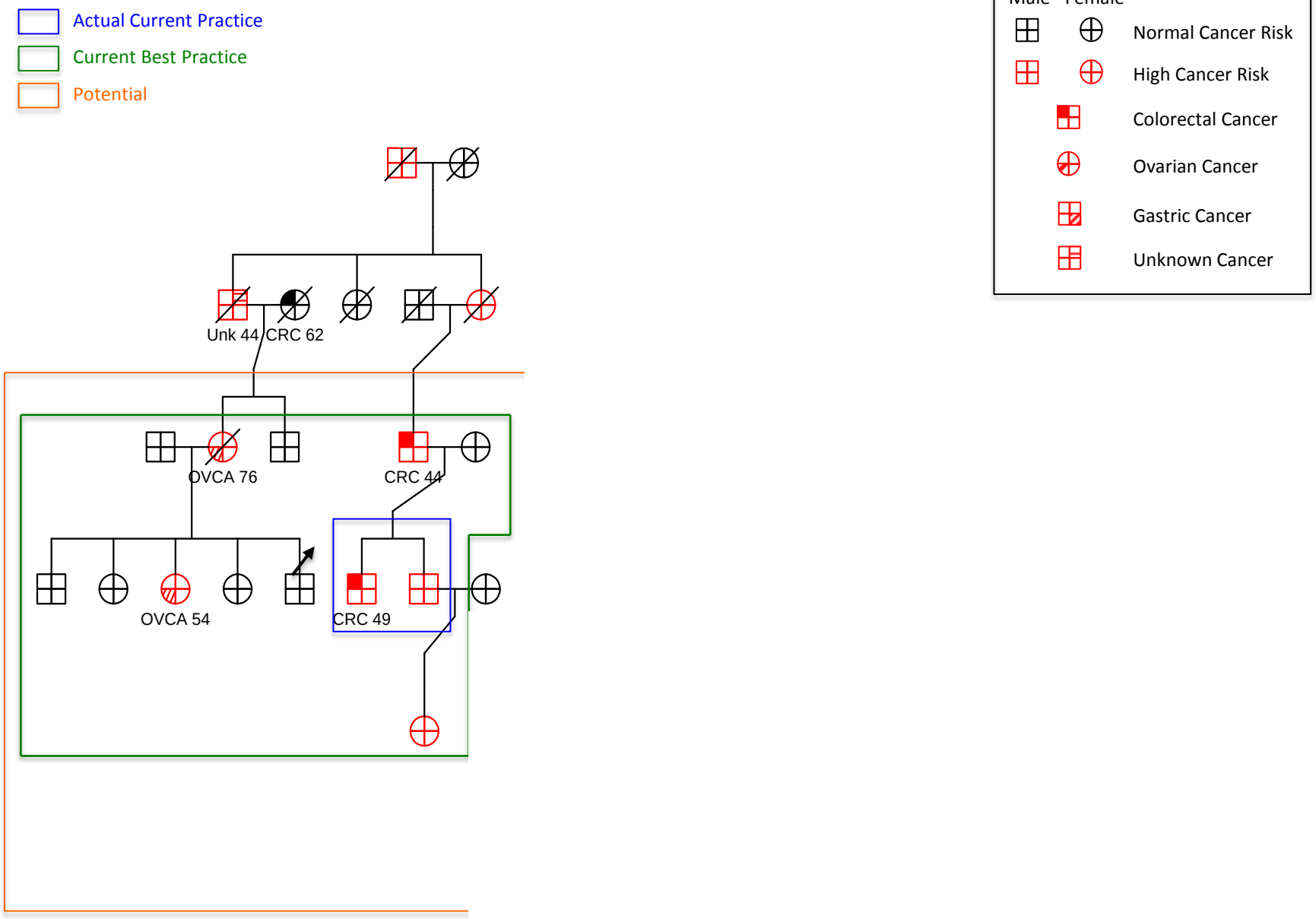


Illustration of different scenarios for cascade screening for in a realistic example pedigree with Lynch Syndrome, the most common hereditary colorectal cancer syndrome.



bioethics

Bioethics ISSN 0269-9702 (print); 1467-8519 (online) doi:10.1111/bioe.12

THE DOUBLE HELIX: APPLYING AN ETHIC OF CARE TO THE DUTY TO WARN GENETIC RELATIVES OF GENETIC INFORMATION

MEAGHANN WEAVER

"Documented reasons [to not share genetic information with relatives] include knowledge barriers such as poor recall of the genetic information or misunderstanding health implications for relatives; attitudinal reasons such as a belief that genetic test do not warrant disclosure, reluctance to deliver bad news, or emotional difficulty discussing the topic; and social reasons such as family conflict, concern for revealing nonparentage, a sense that this is not the appropriate time for disclosure, socially distant relationships; and practical barriers such as difficulty locating family members."

How Personalized is Your Medicine?

"Because we know about the most important risk variant in your family, we know that your outcome will be similar to that of your mother, your brother, and your aunt"

3. FAMILY HEALTH HISTORY IS VITAL TO UNDERSTAND FAMILY-SPECIFIC VARIANTS

3.23483×10^{9}

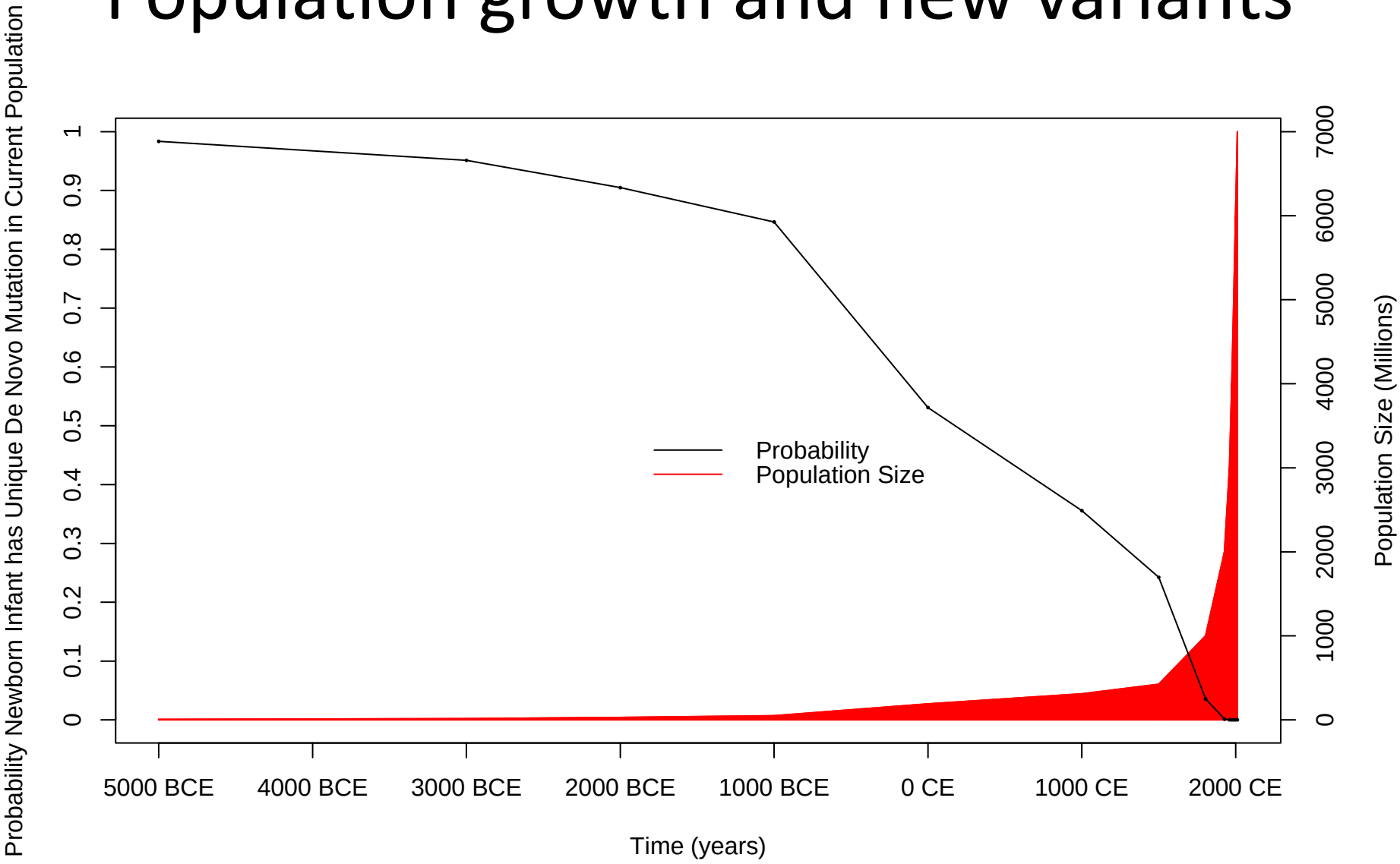
9.70449×10^{9}

$$7.330 \times 10^{9}$$

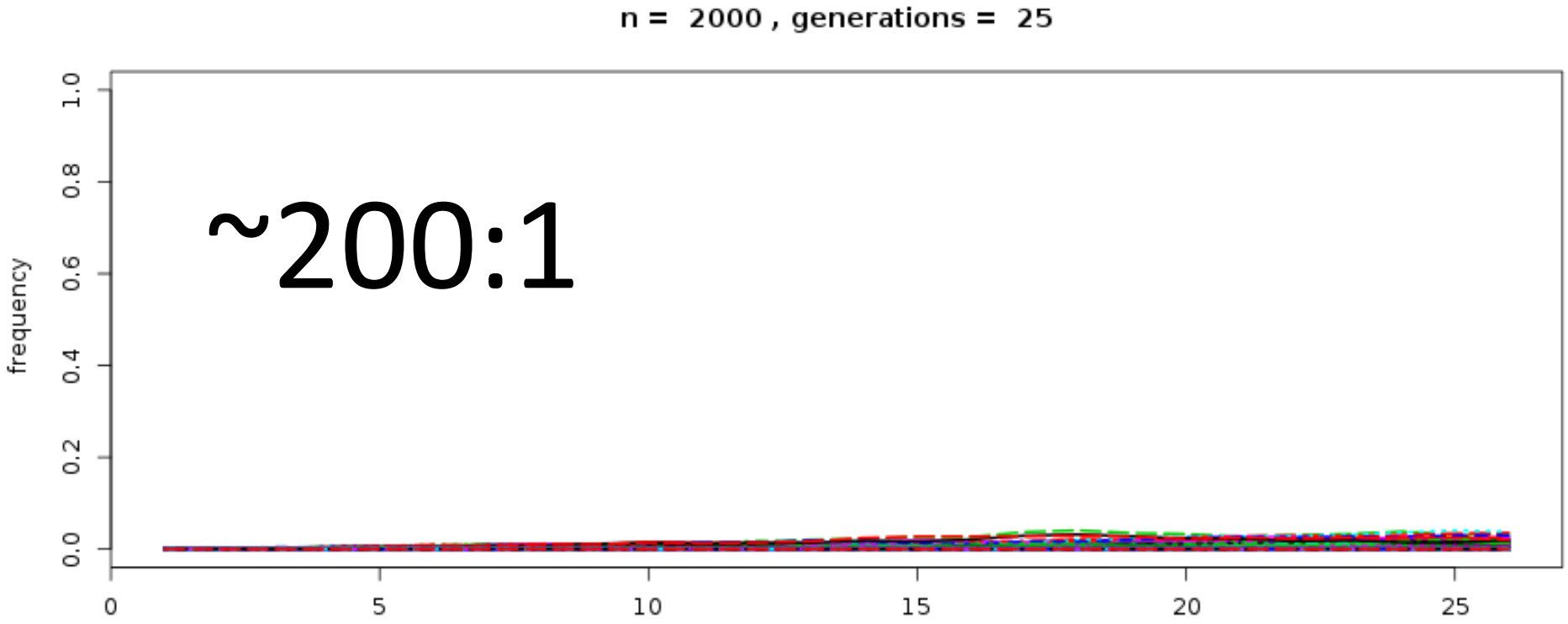
$$1.6 \times 10^{-8}$$

P. F. Palamara *et al.*, *Am J Hum Genet* **97**, 775-789 (2015).

Population growth and new variants



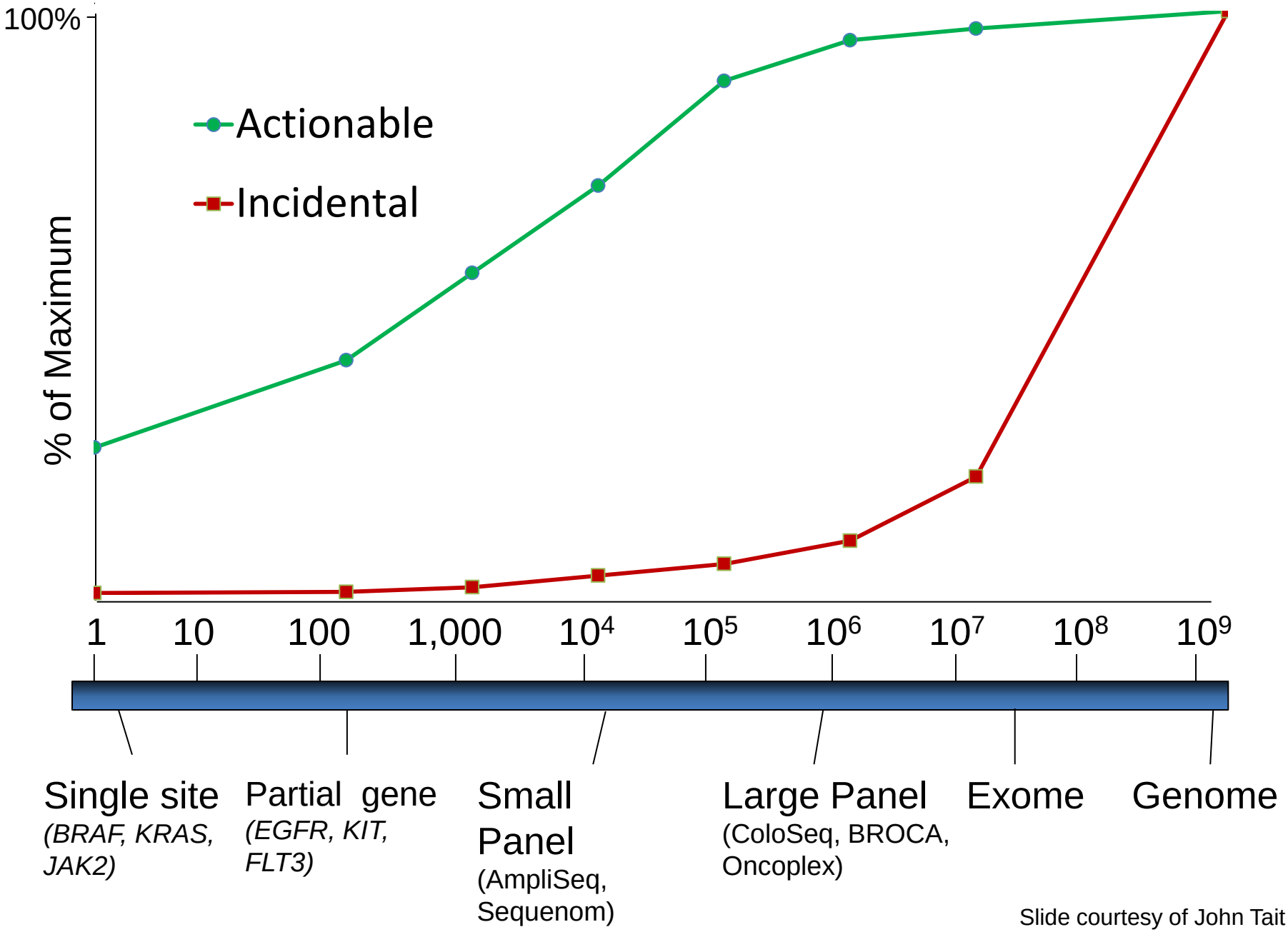
“Family Specific” Variants and De Novo Variants



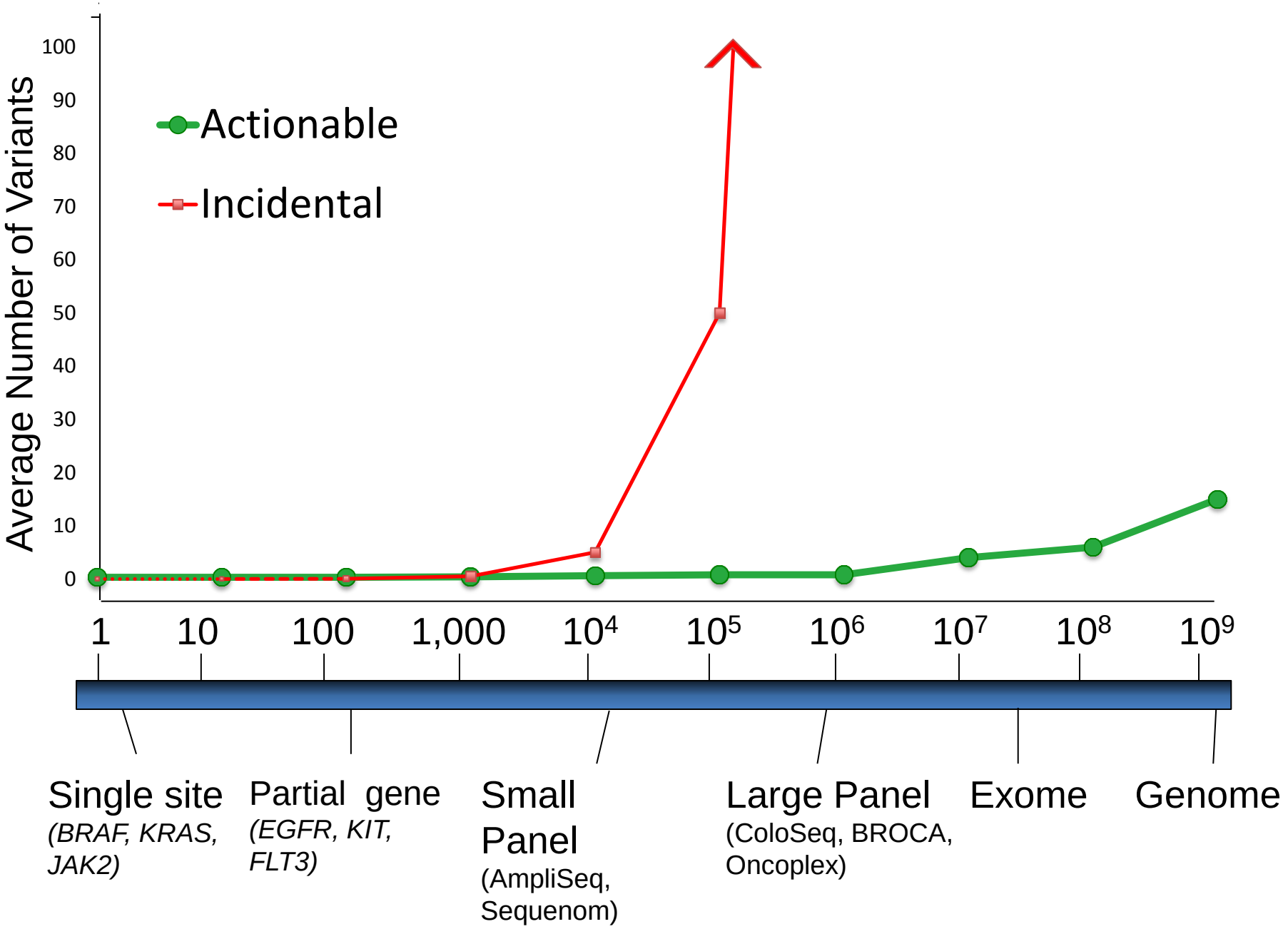
~200:1

The frequencies 20,000 variants that initiated 25 generations ago.
They are almost all extremely rare.

Julin Maloof Lab UC Davis: http://malooflab.phytonetworks.org/apps/genetic-drift-binomial/



Slide courtesy of John Tait and Colin Pritchard

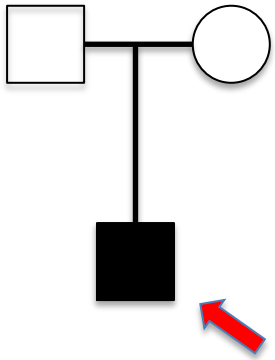

Average Number of Variants
100
90
80
70
60
50
40
30
20
10
0
Actionable
Incidental
1
10
100
1,000
10^4
10^5
10^6
10^7
10^8
10^9
Single site
(BRAF, KRAS, JAK2)
Partial gene
(EGFR, KIT, FLT3)
Small Panel
(AmpliSeq, Sequenom)
Large Panel
(ColoSeq, BROCA, Oncoplex)
Exome
Genome

Family History—the future of personalised medicine?

- Strategies to classify extremely rare variants
  - *In silico* predictions
    - Positive predictive value of CADD < 0.01 in gene panels
  - Functional studies
    - Domain specific
    - Validation sets limited
  - Population studies
    - Feasible only for relatively common variants
  - Family-based co-segregation analysis
    - Robust for all types of variants
    - Relatively large family may be necessary
- Family history is a key to interpreting rare variants

C.A. Mather *et al* 2016, L. M. Starita *et al* 2015, T. A. Peterson*, et al* 2013

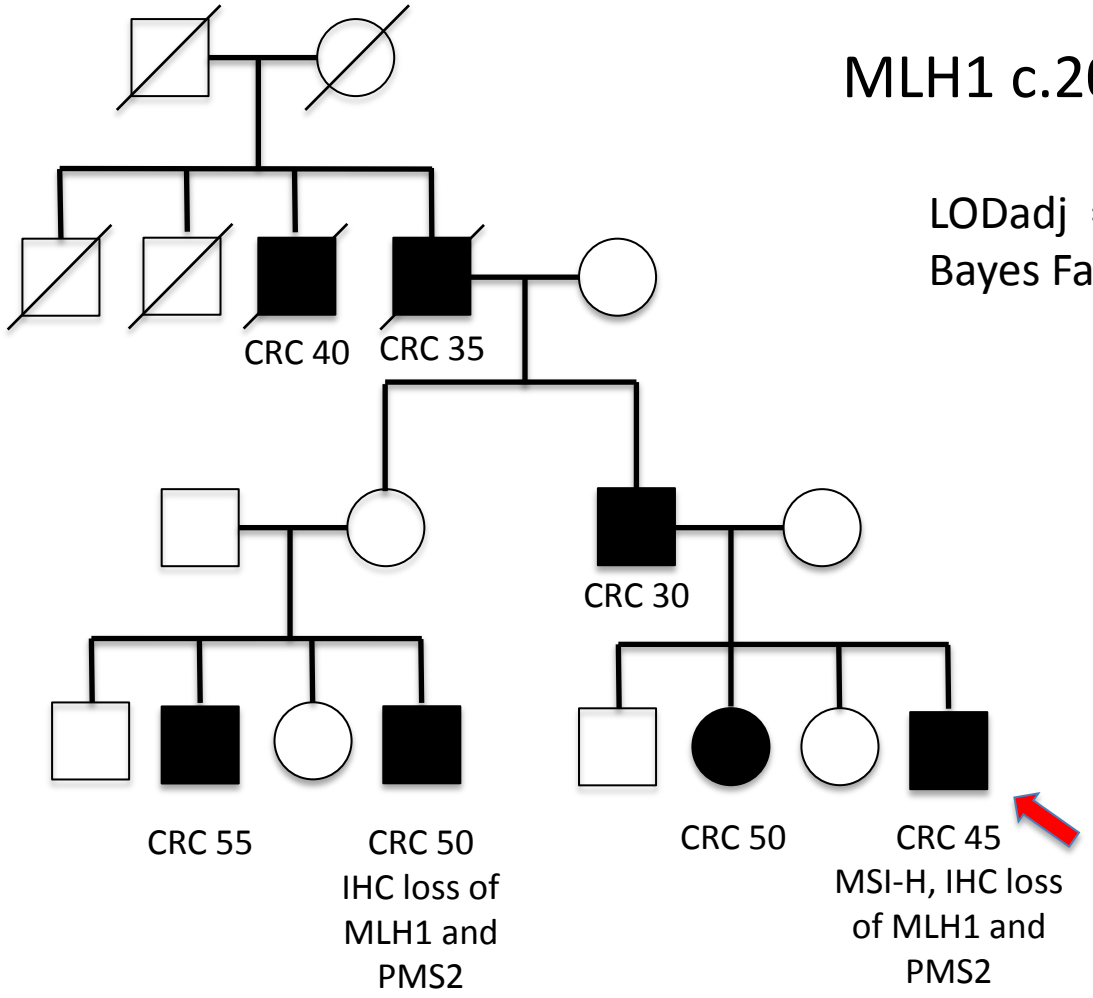
FH vs. No FH: Example 1



CRC 45
MSI-H, IHC loss of MLH1 and PMS2

MLH1 c.207+5G>C

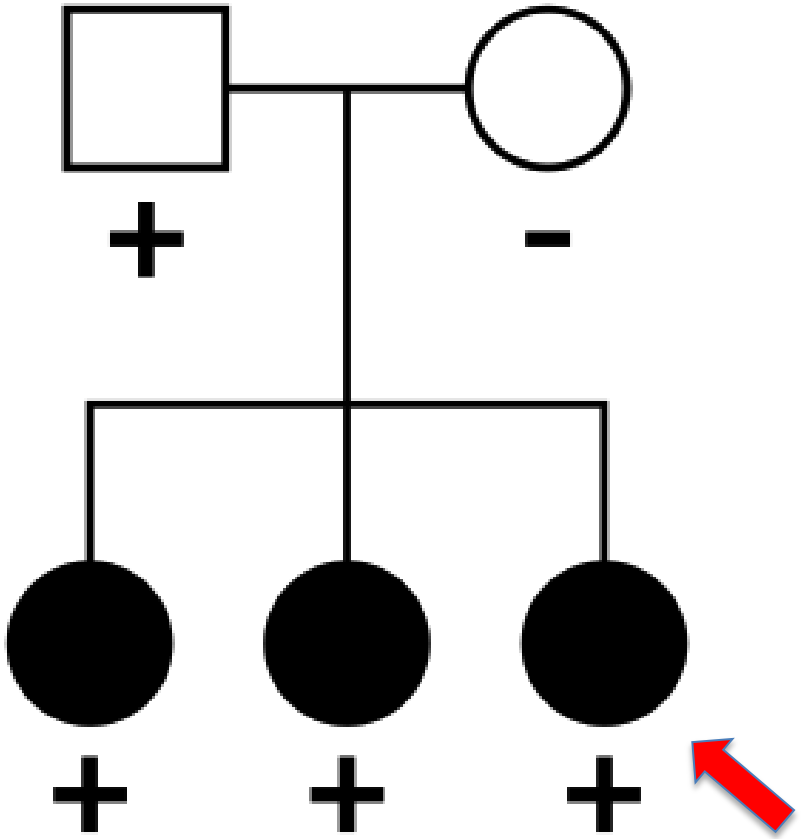
FH vs. No FH: Example 1

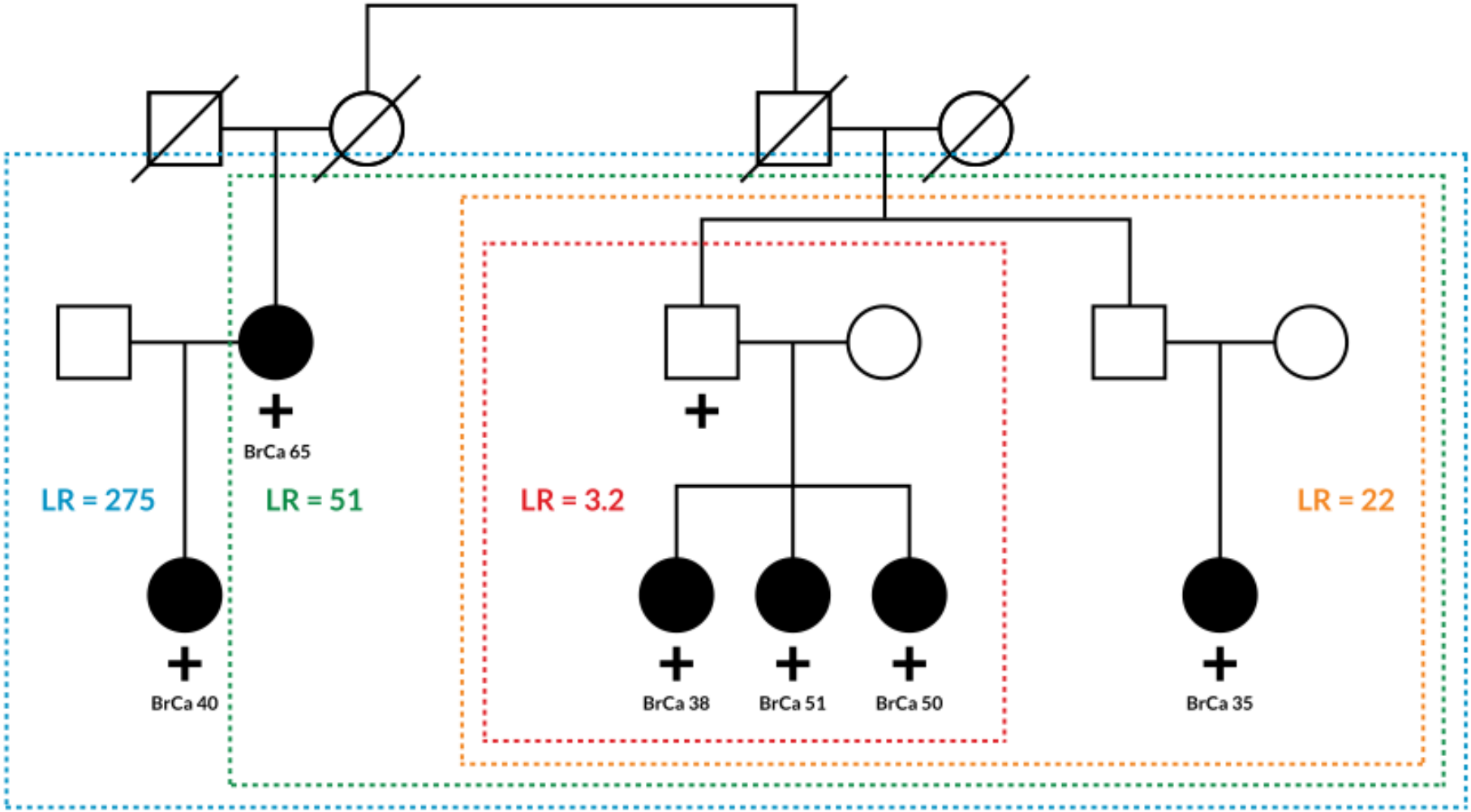


MLH1 c.207+5G>C

LODadj = 1.4
Bayes Factor = 25

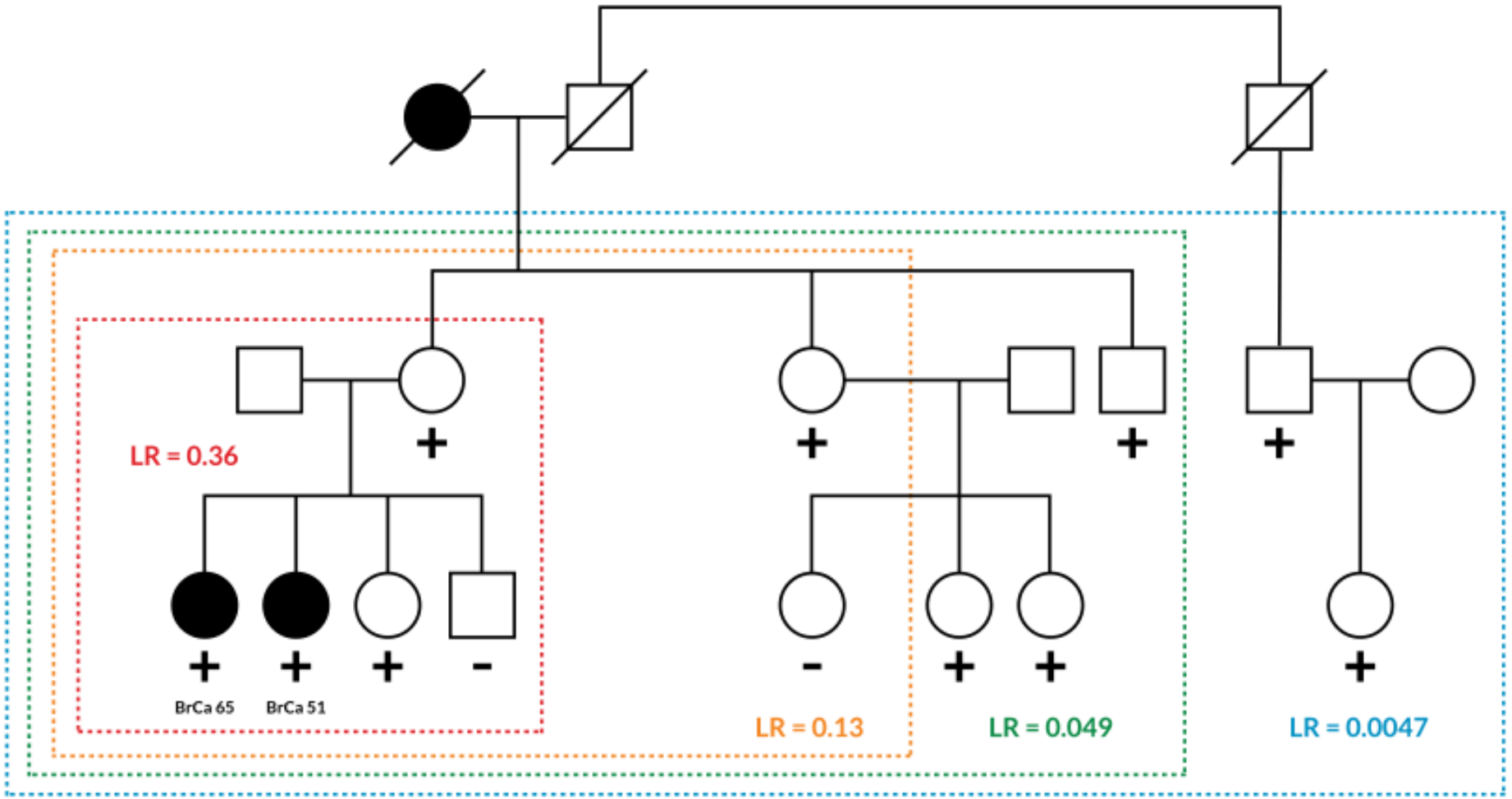
Family-Based Co-Segregation Analysis





Example illustrating how distant family members are more powerful than first-degree relatives In classifying a yet-to-be classified BRCA1 variant.

Findmyvariant.org



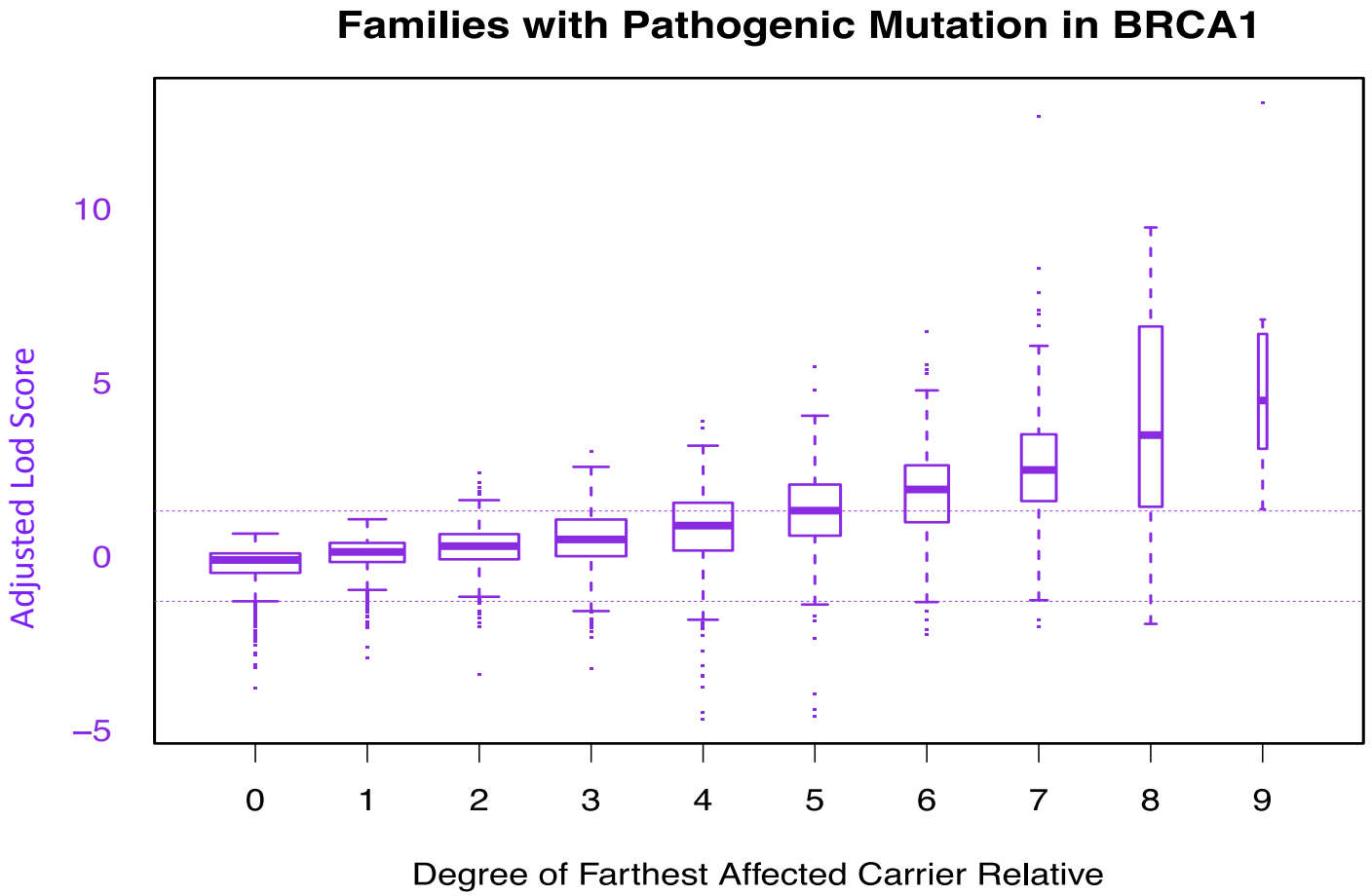
Example illustrating how distant family members are more plentiful than first-degree relatives in classifying a yet-to-be classified benign variant.

Findmyvariant.org

Who should be genotyped

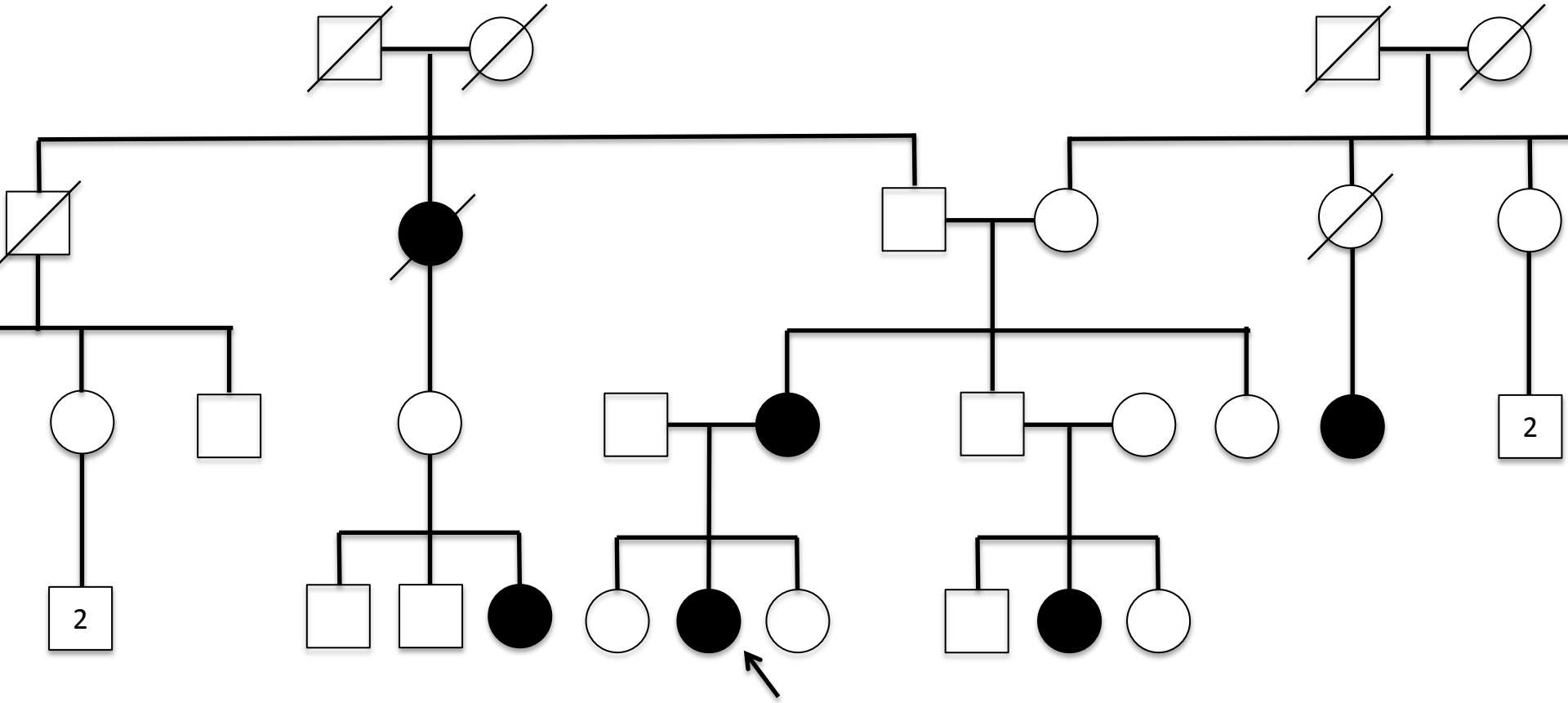
- Anyone who has the disease in question
- Anyone who has a high probability of having the variant in question
  - Regardless of whether they have the disease!

More Family History Allows Greater Power to Understand Family Specific Variants



Shirts and Rosenthal, 2015

Bigger families are better..



but what can you do about it?

FindMy
VARIANT

WHAT IS A VUS OUR GOALS EXAMPLES

Did your genetic testing identify a Variant of Uncertain Significance (VUS)?

Do you want more information on what this variant means for you and your family?

With your family's help you can discover more about your genetic variant.

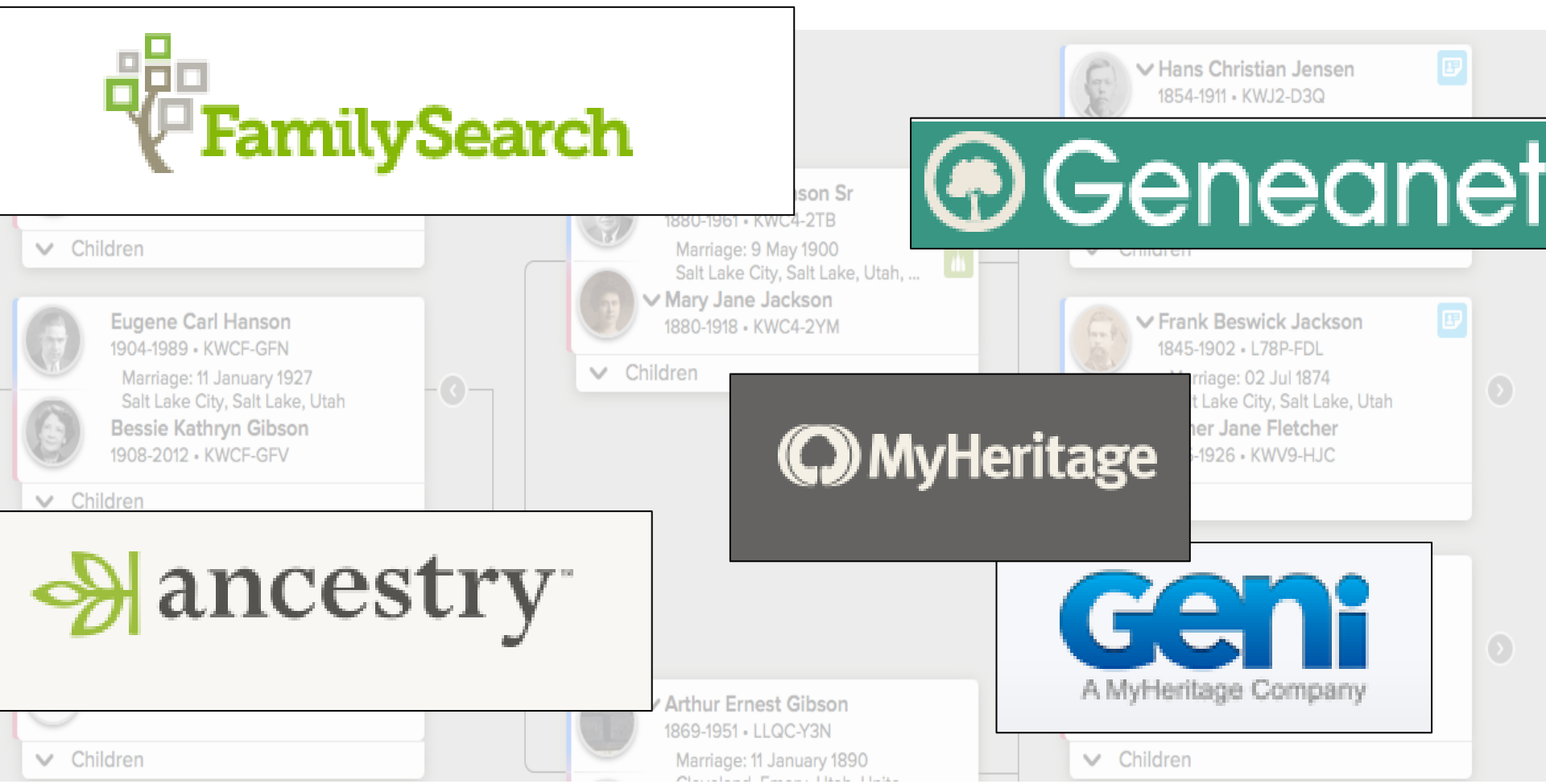
Find your variant in your family.

Get Started

ABOUT US OUR SUPPORTERS CONTACT A GENETIC COUNSELOR ADDITIONAL RESOURCES

PRIVACY STATEMENT TERMS OF USE DISCLAIMER CONTACT US

Tools for Growing Family History: Genealogy



Tools for Growing Family History: Social Networking

A new paradigm for genomic medicine

"I'm going to write you a prescription to get on facebook and contact your 2nd cousin once removed"

The Future of Genomic Medicine

- Better integration of larger, better organized, identifiable family history information into the EHR
- Linking genomic information with family history may be useful for cascade testing
- Translation of family cosegregation studies and other methods for variant classification from research protocols to clinical services.
  - Patient engagement will be key

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Key points

- 1. FHH is vital and not properly used.
- 2. FHH is complementary to genetic analyses
- 3. Should FHH be a gate way for sequencing?
- 4. FHH use in resource limited settings?
- 5. Creation of data bases with FHH and genomic data – very powerful for discovery and development of more robust risk algorithms
- 6. Patient engagement is key